REMARKS

Attached hereto is a marked-up version of the changes made to the specification by the above amendment. The attached page is captioned **"Version with markings to show changes made."**

The above amendments to the specification is directed to more clearly denote various trademarks as recited in the instant application. There is also one change to correct a typographical error. No new matter has been introduced and entry of the amendment is respectfully requested.

Declaration

A new declaration as been required because the declaration filed September 1, 2000 has been asserted as

1) not adequately identifying the instant application; and

2) not referring to the preliminary amendment filed February 28, 2001.

Applicants respectfully traverse because the declaration filed September 1, 2000 contains adequate identifying information in the form of the title of the instant application, the filing date of April 21, 2000, and the attorney Docket No. for the instant application. Moreover, the declaration claims benefit of priority from the same provisional application (60/130,519) as the instant application. These were the items known to the Applicants when the declaration was prepared for execution. As such, the declaration is no different from a declaration executed and submitted on the day after an application is filed, when the application serial number is not yet known. A declaration that includes a reference to the serial number is thus not required for adequate identification or compliance with the statutory requirements of a declaration.

As for a reference to the preliminary amendment filed February 28, 2001, the filed declaration is only directed to the application as filed on April 21, 2000 and does not include within its scope the preliminary amendment of February 28, 2001. Therefore, there is no reason, and no requirement, that the declaration refer to a subsequent amendment. The identification of the amendment as "preliminary" refers to the fact that it was submitted prior to the start of examination on the merits.

Therefore, Applicants respectfully submit that no new declaration is needed because the filed declaration adequately identifies the instant application. Applicants request the withdrawal of this requirement.

Specification

The use of various trademarks in the specification has been more clearly identified by the amendments made above. Generic terminology, as it pertains to the actual composition of the subject matter of the marks, has already been provided in the instant application as filed. Applicants respectfully submit that no further issue remains with respect to the use of marks in the instant application.

Drawings

Figure 1 has been objected to because "the picture covers the label identifying the drawings." Applicants respectfully request that this objection be held in abeyance pending indication of allowance of the instant application because current Figure 1 is a photocopy of a photograph which fails to show how the label is actually clearly depicted in the Figure. Submission of the photograph as part of the formal drawings will demonstrate this point.

Rejection under 35 U.S.C. § 112

Claims 1-3 and 13-14 have been rejected under 35 U.S.C. § 112, second paragraph due to the terms "BPA-MA, EA6 or B3" in claim 14. Applicants respectfully traverse.

As an initial matter, Applicants respectfully point out that the first of the three quoted designations from claim 14 is actually "BPD-MA", which is also discussed on page 10, line 10 through page 11 of the instant specification. This passage also contains more discussion of the photosensitizers identified by the other two designations from claim 14 as well as the structures of all three photosensitizers either by structure or reference to issued U.S. Patents.

As the Examiner is no doubt aware, the claims are to be read in light of the specification, which in this case makes clear and unambiguous the nature of the photosensitizers referred to in claim 14. Thus the claims are not indefinite and withdrawal of the instant rejection is respectfully requested.

Claims 2, 4-7 and 10-15 have been rejected under 35 U.S.C. § 112, first paragraph for failure to enable the prevention or inhibition of "the development of metastatic cancer." Applicants have carefully reviewed the rejection and respectfully traverse.

The rejection asserts that the specification only provides disclosure relating to the treatment of cancer rather than the prevention of "metastatic cancer." The rejection then proceeds to cite Hartwell et al. and Jain for the notion that there are many factors involved in cancer and thus efficacious methods to prevent or inhibit cancer would be "impossible".

Applicants respectfully point out that the actual nature of metastatic tumors as encompassed by the claims and discussed in the application has not been fully appreciated. Claim 2 is directed to "preventing or inhibiting the development of metastatic tumors" which indicates that there was one or more pre-metastatic tumor present in the subject to be treated. The nature of the invention as encompassed by claim 2 is that any tumor cells with metastatic potential that have migrated away from the one or more pre-metastatic tumor may be targeted by the disclosed methods and prevented or inhibited from developing into a metastatic tumor. This point is even more strongly emphasized in claim 4, where the subject has already undergone cancer or tumor therapy, indicating the presence of tumors in the subject prior to the claimed methods.

While the Examiner is correct in that "tumors" and "cancer" are of course related, the present invention provides a means of targeting cells with metastatic potential before they develop into tumors. This is likely different from the concept asserted by the Examiner wherein "metastatic cancer" as a generic concept is being prevented or inhibited.

The efficacy with which the present methods treat metastatic tumor cells (see Example 3 on pages 29-30) provides sufficient guidance for the skilled person to use the present methods to make and use the methods of claim 2 without undue experimentation because efficacy against such metastatic cells and pre-existing knowledge of efficacy against pre-metastatic tumor cells indicates that the methods can target and prevent or inhibit metastatic cells from developing into metastatic tumors.

The reliance on Hartwell et al. and Jain do not alter the above because their disclosures are directed to situations other than those of the instant application and without benefit of knowledge of the inventions and discoveries of the instant application. Thus their teachings do not demonstrate non-enablement of the instant claims in an appropriate manner. Moreover, and

to the extent that the Examiner asserts that no cancer prevention or inhibition is possible, Applicants respectfully point out the large number of public health policies directed to reducing the occurrence of cancer by changing diets and altering behavior (such as cessation of smoking). The ability of such multi-component changes to reduce the occurrence of cancer certainly supports the notion that there is a significant level of understanding in the art concerning many of the factors alluded to by the Examiner.

Applicants thus respectfully submit that the claims are enabled and the rejection may be properly withdrawn.

Prior art rejections under 35 U.S.C. § 102 and 103

Claims 3, 5-9, 11, and 13-16 have been rejected under 35 U.S.C. § 102(b) as anticipated by Korbelik et al. Applicants have carefully reviewed the statement of the instant rejection as well as the cited reference and respectfully traverse the rejection as failing to have presented a *prima facie* case of anticipation.

Instant claim 3 is directed to methods comprising administration to "a subject clinically diagnosed with a primary tumor" while Korbelik et al. is directed to the treatment of transplanted tumors in mice. The scope of claim 3 thus does not include the mice treatments of Korbelik et al., and the rejection fails to provide a single reference which meets all the limitations of the instant claims. A *prima facie* case of anticipation thus has not been presented, and the rejection may be properly withdrawn.

Claims 1, 5-9, and 11-16 have been rejected under 35 U.S.C. § 102(b) as unpatentable over Korbelik et al. Applicants have carefully reviewed the statement of the instant rejection as well as the cited reference and respectfully traverse the rejection as failing to have presented a *prima facie* case of obviousness.

The instant reference by Korbelik et al. is the same as that relied upon above. However, the instant claims are directed to the treatment of "metastatic tumors" which are not the same as the non-metastatic tumors treated by Korbelik et al. In addition to the simple fact that metastatic cancer cells differ from other tumor cells by having been able to migrate away from a primary tumor, escape immunosurveillance, cross various tissue and membrane barriers, implant into new non-tumor burden tissue, and then proceed to develop into a tumor, if treatments of non-

metastatic tumor cells are immediately effective for the treatment of metastatic tumor cells, then why is the mortality due to metastatic tumors so much greater?

The simple answer is that non-metastatic and metastatic tumor cells are not the same and the ability to treat the former does not provide any reasonable expectation of the ability to treat the latter. Without a reasonable expectation of success, there is no *prima facie* case of obviousness presented in the instant assertion that it would be obvious to use the methods of Korbelik et al. on metastatic tumors. Applicants respectfully submit that the instant rejection may thus be properly withdrawn.

Conclusion

In light of the above amendments and remarks, Applicant respectfully submits that claims 1-16 may be indicated as allowable, and early indication to that effect is urged. The Examiner is welcome to contact the undersigned if she determines that further discussions would prove useful.

In the event that the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **273012011100**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: August 10, 2001 By: _____

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Version with markings to show changes made.

In the Specification:

Kindly amend the Specification as follows:

Please substitute the following paragraph for the paragraph on page 7, lines 9-15 of the application:

--New adjuvants, such as the [Ribi Adjuvant System] RIBI ADJUVANT SYSTEM™ (RAS) have been designed to substitute highly purified bacterial components for *M. tuberculosis* in order to maintain the immune stimulatory properties of CFA without the side effects. A variation of RAS, [Detox] DETOX™ adjuvant, is currently in clinical trials as a component of cancer vaccines (NCI-V98-1489, NCI-96-C-0139). Others, such as Hunter's [TiterMax] TITERMAX™, which is has not been approved for clinical use but has been extensively characterized in animal systems, use completely synthetic compounds.--

Please substitute the following paragraph for the paragraph on page 12, lines 1-11 of the application:

--The methods of the present invention may be practiced with any immuno-adjuvant or combination of immunoadjuvants, including those set forth in Appendix A. Particularly preferred immuno-adjuvants are those of microbial or crustacean (chitosan) derived products. These include the [Ribi Adjuvant System] RIBI ADJUVANT SYSTEM™, Detox™, glycated chitosan, and TiterMax™. The [Ribi Adjuvant System] RIBI ADJUVANT SYSTEM™ and its components are described in issued US Patents 4,436,727 and 4,866,034. Preferably, the immuno-adjuvant comprises a mycobacterial cell wall skeleton component (described in US patent 4,436,727) and a component derived from lipid A of a bacterial lipopolysaccharide. Most preferably, the lipid A component is de-3-O-acylated monophosphoryl lipid A (described in US Patent 4,912,094. Additional adjuvants for use with the present invention include CFA, BCG, chitosan, and IFA. Delivery of the immuno-adjuvant may be systemic or localized.--

Please substitute the following paragraph for the paragraph on page 29, lines 3-14 of the application:

--PDT treatment of mice bearing the B16-F1 tumor was performed as previously described for the M1 rhabdomyosarcoma mouse tumor (Richter *et al.*, 1987; Richter *et al.*, 1988; Richter *et al.*, 1991). Each mouse was weighed, warmed under infrared light for less than 5 min to dilate the blood vessels, restrained, and injected intravenously (tail vein) with Verteporfin at a concentration of 1.0 mg/kg body weight using a 28G needle. Thirty minutes later, animals were restrained and half of the animals were injected intratumorally with 50 μL of [Titermax] TITERMAX™ adjuvant (Sigma) prepared as an emulsion with sterile phosphate buffered saline (PBS) according to the manufacturers specifications. Animals were then exposed to a light dose of 100 J/cm^2 in a circular area encompassing the tumor of 1 cm diameter at 688 nm wavelength. The power density was 70 mW/cm^2 and resulted in treatment times of 24 min per animal. Following treatment, animals were monitored daily for tumor response.--

Please substitute the following paragraph for the paragraph on page 31, lines 25-26 of the application:

--The assays may be performed using the commercial, experimental adjuvant, [Ribi Adjuvant System] RIBI ADJUVANT SYSTEM™ (RAS) (Corixa) or [Detox B-SE] DETOX B-SE™ (Corixa) and alum for comparison.--

Please substitute the following paragraph for the paragraph on page 32, lines 11-17 of the application:

--Liposomal verteporfin is injected at a dosage of 14 mg/m2 of body surface area, which is a higher dose than for treating AMD. One to three hours later, diode laser light is applied at a rate of approximately 200mW/cm2 for a total dosage of 120-180J/cm2 to the lesion being treated. The dosage of the [Detox] DETOX™ adjuvant, which is injected into the lesion after PDT, provides in the range of 100-200μg of the cell wall skeleton component, and 20-30μg of

the monophosphoryl lipid A component. This procedure is carried out at approximately 2 week intervals. [Perferably] Preferably there are 3 treatments.--

Please substitute the following paragraph for the paragraph on page 43, lines 22-27 of the application:

--i. **[Ribi Adjuvant System] RIBI ADJUVANT SYSTEM™ (RAS)**
4 components: (1) monophosphoryl lipid A (MPL); (2) trehalose dimycolate (TDM); (3) cell wall skeletons (CWS); (4) *S. typhimurium* mitogen (STM)
Ribi ImmunoChem Research, Inc.
http://www.ribi.com/--

Please substitute the following paragraph for the paragraph on page 44, lines 8-13 of the application:

--v. **[Detox B-SE™] DETOX B-SE™** for investigational use is supplied in clear glass vials.

Each vial contains: 145 micrograms CWS from M. phlei, 25 micrograms MPL from S. minnesota R595, 8.1 milligrams Squalane F, 0.38 milligrams Polysorbate 80 (USP/NF), 1.62 milligrams Soy Lecithin (NF), and 88 micrograms Sterile Water for Injection (USP)

[Detox B-SE] DETOX B-SE™ must be stored refrigerated between 2 and 8°C--

Please substitute the following paragraph for the paragraph on page 45, lines 9-11 of the application:

--i. **[TiterMax] TITERMAX™**
CytRx Corporation
http://www.cytrx.com/--